Review of Evidence on Antimicrobial Resistance and Animal Agriculture in Developing Countries

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Acronyms

AMR	Antimicrobial resistance
CDC	Centres for Disease Control and Prevention
DALY	Disability adjusted life year
EU	European Union
ESBL	Extended spectrum beta lactamase
FAO	Food and Agriculture Organization
IFAH	International Federation for Animal Health
LA-MRSA	Livestock associated methicillin resistant *Staphylococcus aureus*
MRSA	Methicillin resistant *Staphylococcus aureus*
NTC	Non typhoidal *Salmonella*
NCV	Non cholera *Vibrio*
OIE	World Animal Health Organization
UK	United Kingdom
WHO	World Health Organization

Executive summary

This short paper aims to identify key evidence gaps in our knowledge of livestock- and fisheries-linked antimicrobial resistance in the developing world, and to document on-going or planned research initiatives on this topic by key stakeholders.

The antimicrobial resistant (AMR) infections in animals that are of most potential risk to human health are likely to be zoonotic pathogens transmitted through food, especially *Salmonella* and *Campylobacter*. In addition, livestock associated methicillin resistant *Staphylococcus aureus (LA MRSA)* and extended spectrum beta lactamase *E. coli* (ESBL *E. coli*) are emerging problems throughout the world.

In developing countries, AMR pathogens are commonly found in animals, animal food products and agro-food environments, but the lack of surveillance systems means there are no reliable national data on the level of AMR in animals and their products. **While AMR pathogens in animals and their products undoubtedly contribute to AMR infections in people, the literature from developing countries is insufficient to draw firm conclusions on the extent of this contribution.**

The key driver of agriculture-related AMR is the quantity and quality of use of antimicrobials in livestock production and aquaculture. **We don't have accurate information on antibiotic use in developing countries** but agricultural use probably exceeds medical use; most use is probably in intensive production systems; and, use is probably increasing rapidly.

The underlying driver for antimicrobial use and development of AMR is the livestock and aquaculture revolutions, by which is meant the rapid growth in intensive production systems in response to increased demand for livestock and fish products. This demand in turn is driven by population increases, urbanisation, improving economic conditions and globalisation in developing countries and is predicted to continue to increase. Based on livestock intensification patterns, China, Brazil and India are current hotspots, and future hotspots are Myanmar, Indonesia, Nigeria, Peru and Vietnam. Based on aquaculture trends, China is a hotspot and Indonesia, Thailand, Vietnam, Bangladesh, India and Chile are other countries where antimicrobial use in fish production may be problematic.

Many interventions using educational, managerial, regulatory and economic approaches to improve drug use have been studied. Training by itself is relatively ineffective but if combined with strategies to change market conditions (by changing incentives and accountability environment) better success has been achieved. There are many animal husbandry options that can allow production without non-therapeutic antimicrobials, but these options have not been widely used in, or adapted to, developing countries.

In developing countries, there is a dearth of evidence on most aspects of agricultural related AMR. This includes: the use of antimicrobials in agriculture; the impacts of this use on human and animal health; the acceptability and feasibility of stricter control of antibiotic use in agriculture; and, the costs and benefits of stricter control taking into account trades offs between overuse and lack of access to antimicrobial drugs. At the same time, AMR is intrinsically a global problem that can only be managed at supra-national scale and the current strong momentum to take action on AMR provides an opportunity to address the problem globally and comprehensively, addressing both medical and veterinary use. This should be done in an evidence-based way which includes filling knowledge gaps, careful piloting of interventions, and rigorous evaluation of successes and failures.

SECTION 1

Introduction

Human infections caused by pathogens that have become resistant to the medical drugs impose a large burden of illness and death and entail enormous costs. Recent reports predict drug resistance will increase substantially, causing millions of extra deaths and costing trillions of dollars by mid 21st century (see section 4). While many disease-causing organisms show resistance to drugs **this report focuses on infections caused by bacteria that are potentially linked to agricultural use of antibiotics in developing countries.**

Bacterial infections in people and animals have been successfully treated with antimicrobials[1], since the discovery of these drugs in the first half of the 20th century. However, the use of antimicrobials in animal agriculture (both livestock and fish production) has been debated for decades because of its potential impacts on human health. In recent years there is increasing consensus that there are links between veterinary drug use and drug resistance in human pathogens, and that it is desirable to reduce antimicrobial use in agriculture.

Agriculture is of crucial importance for food security and development. Worldwide, one in three people work in agriculture and farming produces 4 billion tonnes of food to feed over 7 billion people a year. Rising populations in developing countries, alongside increasing wealth, urbanisation and changing dietary preferences are driving a dietary revolution, in which consumption of eggs, milk, meat and farmed fish is increasing much more rapidly than the consumption of staples or pulses. This in turn is driving changes in how animals are farmed. Poultry, pig and fish production is increasing fastest, and ever more animals are kept in high input-high output intensive systems.

These increases in animal numbers and changes in farming systems, against a background of high levels of endemic and epidemic disease would be expected to increase use of antibiotics in developing country agriculture. Because the quantity of antibiotics used is the main driver of development of resistance to these antibiotics, animal agriculture in developing countries could have an increasing role in the development of antimicrobial resistant (AMR) pathogens. While discovery of novel antimicrobials would support management of infectious bacterial disease into the future, over the last decades there has been a dramatic slow-down in the development of new antimicrobials, which increases the need to safeguard existing antimicrobials.

The report aims to identify key evidence gaps in our knowledge of livestock- and fisheries-linked antimicrobial resistance in the developing world and to document on-going or planned research initiatives on this topic by key stakeholders.

1 Technically, an antibiotic is a substance produced by a microorganism that at a low concentration inhibits or kills other microorganisms and an antimicrobial is any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms (bacteria, virus or other) but causes little or no damage to the host. All antibiotics are antimicrobials, but not all antimicrobials are antibiotics. An antibacterial is a substance used to treat bacterial infections. However, antibiotic is now more often used to signify antibacterial and is understood by the public and professionals this way. In this document, antimicrobial is used but generally refers to antibiotics.

SECTION 2

Key players and initiatives on AMR research and management

International organisations with an interest in research:

- The World Health Organization (WHO) has been addressing AMR since 2001 and is the lead global organisation for tackling AMR. Its numerous activities include assessing AMR, capacity building for AMR surveillance, co-ordinating AMR activities, and developing strategies and action plans. In 2015 the WHO launched the Global Action Plan for AMR.
- The World Animal Health Organization (OIE) promotes prudent use of veterinary drugs, helps harmonise national surveillance programs, and conducts risk assessment. It is developing a global database on veterinary drug use.
- The Food and Agricultural Organization (FAO) has activities on AMR, often as tripartite collaborations with WHO and FAO. This includes providing advice, improving regulatory frameworks, raising awareness and supporting research to generate data.
- The Codex Alimentarius Commission has a longstanding Committee on Residues of Veterinary Drugs in Foods and an ad hoc Intergovernmental Task Force on Antimicrobial Resistance. Principal texts include a code of practice to minimize AMR and guidelines for risk analysis of foodborne AMR.
- The CGIAR system conducts agricultural research for poverty alleviation. A new CGIAR research program on the human health impacts of agriculture has a cluster of activities on antimicrobial use in agriculture.

In addition, many regional actors have an interest in AMR including the European Union, the African Union, the Association of Southeast Asian Nations and others.

"Three sisters' initiatives" for AMR management and understanding
The 'three sisters' can refer to the three sister organisations with a mandate for global health (WHO, OIE and FAO) or to the three standard setting organisations recognised by the World Trade Organization (the Codex Alimentarius Commission, OIE and International Plant Protection Convention). Initiatives on AMR involving WHO, OIE and FAO include:

- The Global Foodborne Infections Network (GFN) is a WHO initiative to build laboratory capacity and provides training and reference facilities for AMR pathogens.
- The WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) was set up in 2008 to minimize the public health impact of AMR associated with the use of antimicrobial agents in all food-producing animals.
- WHONET is a downloadable, Windows-based database software used for the management and analysis of microbiology data, with a special focus on the analysis of antimicrobial susceptibility test results.
- The Antimicrobial Resistance Information Bank (AR InfoBank) provides access to policy-makers and health care workers to information about drug resistance and resistance surveillance networks. It is collaboration between WHO and WHO Collaborating Centre for Electronic Disease Surveillance, INSERM, Paris.

- The FAO/OIE/WHO Tripartite is a formal alliance to enhance collaboration between human and animal health and has identified AMR as one of the three priority topics for joint actions.

***Developing country stakeholders*:**
These include public and private health services and veterinary services which use, and in the case of public services, regulate antibiotics; food safety authorities concerned with antimicrobials as health hazards; research institutes who carry out most of the studies on AMR; consumer groups concerned with food safety (but often ineffective); large-scale commercial agriculture and aquaculture who are major uses of antimicrobials; NGOs who often provide treatments for animals after disasters or in vulnerable communities; and small-scale farmers who are likely minor users of antimicrobials.

Veterinary pharmaceutical companies and representatives:
The largest global companies are Zoetis, Merck Animal Health/MSD Animal Health, Bayer HealthCare Animal Health Division, Virbac s.a. and Elanco Animal Health.There are many veterinary drug manufacturers in developing countries; these tend to produce generic drugs and are less organised into groups representing their interests. The International Federation for Animal Health (IFAH) represents the animal health industry (but mainly developed world companies). Globally, the investment of private pharmaceutical firms into research and development is around double the investments of the public sector, and most of this investment is for human health products. However, there is very little research into bacterial infectious diseases other than tuberculosis.

Other initiatives with a global perspective):
The following initiatives (in alphabetical order) have a focus on both veterinary use of antibiotics and developing countries:

- Antibiotic Action (AA) is a global initiative established by the British Society for Antimicrobial Chemotherapy (BSAC) as a forum to identify and implement solutions for AMR.
- Founded in 1981, the Alliance for the Prudent Use of Antibiotics (APUA) is the oldest of the organisations devoted to protecting antibiotics. It began including developing countries in Latin America and then Africa in its formal network around the turn of the 21st century.
- The Global Alliance for Livestock Veterinary Medicines (GALVmed) is a not-for-profit public-private partnership that aims to increase availability and access of livestock products to poor farmers. It has been working with FAO and IFAH on vet drug quality.
- The Global Antibiotic Resistance Partnership (GARP) is a project funded by the Bill and Melinda Gates foundation and implemented by the Center for Disease Dynamics, Economics & Policy (Washington). It generates evidence and formulates and promotes policy related to antibiotic use and resistance in low and middle income countries.
- The Global Health Security Agenda (GHSA) is a USA government initiative with 12 action packages, including the Antimicrobial Resistance Action Package. This helps develop and implement national action plans for AMR. The initiative is led by Centres for Disease Control and Prevention (CDC).
- The International Surveillance of Reservoirs of Antibiotic Resistance (ISRAR) project is coordinated by the Alliance for the Prudent Use of Antibiotics (APUA), to collect and analyse environmental and veterinary commensal organisms which may serve as reservoirs for AMR.
- Action on Antibiotic Resistance (ReACT) is an independent global network for concerted action on antibiotic resistance. Operating from Uppsala University,

Sweden it carries out awareness raising activities in many developing countries and supports national working groups.

- The Review on Antimicrobial Resistance (RAR) is a UK initiative co-funded by, but independent of, the UK Government the Wellcome Trust. By the summer of 2016, the Review will recommend a package of actions that should be agreed internationally.
- The World Alliance Against Antibiotic Resistance (WAAR) is a non-profit organisation comprising a range of stakeholders from over 50 countries which aims to raise awareness on antibiotic resistance.

Surveillance networks with a global or developing country focus:
Many surveillance networks focus on AMR in human pathogens including SENTRY, ANSORP and DOMI in Asia. In Africa, Pasteur Institutes in several countries provide well-functioning laboratories.

Developed country interests:
These include research institutes, donors, food importing companies, veterinary pharmaceutical exporting companies, and government and intergovernmental agencies with interests in global AMR.

Organisations that fund research into AMR
The following organisations were identified by the WHO as providing funding for research on AMR and have interests or a mandate for research in developing countries:

- APUA - Alliance for the Prudent Use of Antibiotics
- Bill and Melinda Gates Foundation
- European Union
- Grantsnet
- ISID - International Society for Infectious Diseases
- The Wellcome Trust
- USAID-The United States Agency for International Development

Organisations that fund research into AMR but without a major focus on developing countries include:

- CDC - Center for Disease Control in the USA
- ESCMID - European Society of Clinical Microbiology and Infectious Diseases
- MRI - Medical Research Council (UK)
- NIAID - National Institute of Allergy and Infectious Diseases
- UK Department of Health
- USDA ARS - United States Department of Agriculture Agricultural Research Service
- USEPA - The United States Environmental Protection Agency

SECTION 3

Prevalence of AMR infections in livestock and fish systems and products

Evidence

Animal infections caused by AMR pathogens of greatest threat to human health are zoonotic pathogens transmitted through food and by direct contact. Among the most common zoonotic pathogens transmitted through livestock and food to humans, are non-typhoidal *Salmonella* (NTS), *Campylobacter,* and toxigenic *Escherichia coli*, (WHO, 2011; WHO, 2014). Livestock are important reservoirs for these three pathogens and AMR is widespread especially in *Campylobacter* and *Salmonella*. All three are important causes of gastro-intestinal illness in developing countries and globally, and are responsible for 27 million Disability Adjusted Life Years (DALYs)[2] annually or 30% of all diarrhoeal DALYs (IMHE, 2013). (For comparison, breast cancer has a burden of 12 million DALYs and hepatitis 13 million). Less common, but important, zoonotic foodborne pathogens include non-cholera *Vibrio* (NCV) in seafood and *Listeria monocytogenes* in meat and dairy products: their global burden has not been well assessed.

AMR is a problem in these five foodborne pathogens in developing countries and the contribution of drug resistant infections to the overall human health burden caused by these diseases, while not well quantified, is probably substantial. However**, less is known about the role that agricultural use of antibiotics plays in the development of this resistance.** Some studies find high resistance levels in pathogens from human clinical cases, alongside low resistance levels to the same antibiotic in pathogens in food-producing animals (or the reverse) suggesting bacterial populations are seperate (Luangtongkum et al., 2009). In other cases, similar resistance patterns are seen in bacteria isolated from animals, people and the environment suggesting shared bacterial populations (Sahoo et al., 2012).

It is highly probable that *E. coli* and enterococci acquired from animal products are a source for resistance plasmids that spread to human adapted *E. coli* and enterococci, causing urinary and wound infections, and septicaemia (EFSA, 2008). The burden of this in developing countries is not known. Genes for a type of resistance known as extended spectrum beta-lactamase (ESBL) and AmpC beta-lactamase have spread internationally over the last decade in strains of *E. coli* and *Salmonella*. ESBL is spread mainly by transfer of plasmids. **The burden of ESBL infections attributable to livestock is not known,** but the frequent prevalence of ESBL/AmpC producing organisms in farm animals and food products suggests they may be the origin of some human infections.

Methicillin resistant *Staphylococcus aureus* (MRSA) is a major cause of human illness worldwide, and is usually acquired directly or indirectly from people. **The burden of MRSA and the prevalence of LA-MRSA in developing countries is not known.** In countries with better data it is generally of minor importance compared to hospital or community acquired MRSA, except for countries with low levels of MRSA and high levels of pig keeping. In these contexts, LA-MRSA infections are usually found in people having contact with pigs (or calves).

[2] The Disability Adjusted Life Year (DALY) is widely used and accepted global metric of human sickness and death. One DALY can be thought of as one lost year of "healthy" life.

We do not have good data on the prevalence of AMR pathogens in livestock and fish and their products in developing countries. This is because systematic, national, iterative (repeated) surveillance programs are needed to generate good information on AMR in livestock, fish and food, and these types of programmes exist only in some EU and north American countries (WHO, 2014).

Many individual studies suggest AMR is common in agricultural systems in developing countries. There are many academic studies that assess antibiotic residues and AMR pathogens in animals, in livestock and fish products, and (to a lesser extent), in agro-food environments, and wildlife in developing countries. Drug resistance is found in zoonotic and non-zoonotic pathogens (see table 1 for examples). Most studies find resistance is common to older, cheaper, widely used antibiotics and often present for newer, more expensive drugs, not licensed or rarely used in veterinary medicine. Resistance to other veterinary drugs such as trypanocides, insecticides and de-wormers are also commonly reported in developing countries. **However, many of these studies have quality problems: weak methodology (e.g. sampling was not random, detailed microbiological methods are not given, no information on quality assurance) and non-standardised reporting; representative of small populations; and, published only in the grey literature.** Only a few more recent reviews cover multiple pathogens and countries (Mshana et al., 2013; Omulo et al., 2014). **Most studies focus on prevalence and patterns in single hosts or food types.**

Population	Disease type / pathogen	Antimicrobial Resistance		Reference
		Older %	Newer %	
Free-ranging pigs, Kenya	Animal (salmonella)	37 (ampi)	4 (cipro)	Onyango et al., 2014
Urban dairy cows, Ethiopia	Zoonoses (NTS)	100 (ampi)	0 (cipro)	Addis et al., 2011
Smallholder chicken, Nigeria	Zoonosis (S. aureus)	100 (ampi)	0 (cipro)	Suleiman et al., 2013
Intensive chicken, China	Zoonosis (E coli)	88 (ampi)	17 (gent)	Wang et al., 2013
Farmed cockles, Malaysian coast	Zoonosis (NCV)	68 (ampi)	0 (cipro)	Sahilah et al., 2014
Salads, retail shops Nigeria	Zoonoses (Listeria)	93 (ampi)	4 (cipro)	Ransangan et al., 2013
Cow dung, India	Zoonoses (E. coli)	71 (ampi)	43 (cipro)	Sahoo et al., 2012

Ampi = ampicillin, cipro=ciprofloxacin, gent=gentamicin

Table 1 Examples of studies on antimicrobial resistance in agri-food systems in developing countries

The large number and consistency of results make it very likely that AMR pathogens are common in animals, animal food products and agro-food environments in developing countries, **but the literature is insufficient to draw firm conclusions on drivers or management of AMR or the contribution of AMR in agricultural systems to AMR illness in humans or animals.**

Evidence Gaps

- There is no continuous, systematic, national surveillance of AMR in animals and their products in developing countries. Surveillance of animals and their products is usually not integrated with AMR surveillance in human hospitals and the community.
- There is no global standardisation for AMR surveillance. The Clinical and Laboratory Standards Institute in the US and EU do not agree on key aspects of measuring AMR, and the introduction of molecular techniques may further complicate comparisons (Vernet et al., 2014).
- Current technologies for AMR surveillance can be expensive and complicated. Molecular diagnostics have the potential to allow rapid detection of resistance and information technology could help in reporting and analysing data and therefore should be supported.
- There is no synthesis of existing studies on agriculture associated AMR that would provide an overview on prevalence, trends, and variation by farming system, species and country. A systematic literature review could summarise and synthesise the considerable information available in the published and grey literature.
- The existing studies on AMR in animals, animal products and animal environments often exhibit methodological weaknesses. It would be useful to have guidelines and checklists for study quality such as are available for other types of epidemiological study.
- There is limited understanding of the sources of AMR in animal agriculture and the relative importance of different sources. This information is needed to target scarce resources to where they can be most useful. Comparative molecular epidemiology studies of human, animal, food and environmental isolates could shed light on this.

SECTION 4

Health and economic impacts of livestock- and fisheries-linked AMR in developing world

Evidence
Information on the health and economic impacts of livestock and fisheries related AMR in developing countries is lacking. This is because there is little and weak information on how much AMR illness in animals or humans is the result of the use of antimicrobials in agriculture.

The previous section summarises the reasonable evidence that despite a lack of good, nationally representative data on presence or levels of AMR pathogens in agriculture, **AMR pathogens are commonly found in agricultural environments, animals and food products in developing countries.** These could and likely do contribute significantly to diseases in humans caused by the same organism. **However, these studies do not provide information on the origin of AMR in pathogens, so it is not known to what extent the presence of AMR in agriculture systems is due to agricultural use of antimicrobials.** Pathogens can show AMR because:

- They are naturally resistant to antimicrobials.
- They have been exposed to antimicrobials and developed resistance due to selection pressure.
- They have acquired resistance factors from other bacteria exposed to antimicrobials as the result of transfer of resistance conferring genes, often by plasmids.

Natural resistance is considered of minor importance (CDC, 2014) so pathogens in animals and their products are mostly likely to develop resistance as a result of exposure to antibiotics through these different pathways:

1. Antibiotics directly given to the animals by injection, or as food/water additives to treat disease, prevent illness or promote growth (important).
2. Antibiotics in the environment resulting from antibiotics given to other animals and then passed in animal faeces and urine, or from discarded feed or contaminated water (probably important).
3. Antibiotics in the environment resulting from antibiotics used to treat humans or companion animals/pets (the latter is probably of minor importance in developing countries) and then passed in faeces or urine to contaminate the environment.
4. Antibiotics in effluents from antimicrobial production (this pathway may be important in some countries).
5. Antibiotics used in plant production (especially fruit trees) or deliberately added to food as a preservative (these are probably minor pathways).

So if an AMR pathogen is found in an animal population, even assuming the pathogen developed resistance in that animal population, we do not know which of five exposure pathways was relevant. **We do not have national estimates of how much veterinary and human antibiotics are used in the five pathways listed above,** (although we suspect some are more important than others), **making it difficult to assess the relative importance of these sources of exposure in creating resistance.** Moreover, when we find an AMR pathogen in an animal population we do not know whether the resistance was generated in the animal population studied or acquired from other animal populations, people, or the environment. :

Because of these complications, there is little evidence to inform the extent to which AMR infections in people in developing countries are acquired from animals, animal products or agro-food environments.

There is some evidence that suggests agricultural use of antibiotics may not have very important human health impacts in developing countries:

- Most experts agree that use of antibiotics in human medicine is by far the major cause of antibiotic resistance in people (Aarestrop, 2005; Olivier et al., 2010; CDC, 2014).
- AMR pathogens are found in livestock that are never given antibiotic treatments e.g. backyard chicken and scavenging pigs, suggesting livestock have acquired infection from people or from exposure to antibiotics in human excreta (Onyango et al., 2014).
- In a recent survey, chief veterinary officers reported African countries used an average 418 tonnes of antibiotics in agriculture each year (Grace et al., in press). This is less than half the amount used by the average OECD country (864 tonnes per year) (van Boeckel et al., 2015) suggesting antimicrobial use in some African countries is not excessive compared to use in OECD agriculture.
- The main human health threats from drug resistance are: malaria; tuberculosis; streptococcus pneumonia; gram negative infections (ESBL *Klebsiella* pneumonia and *E. coli* infections) and MRSA (Vernet et al., 2014). Veterinary drug use is only likely to contribute directly to ESBL gram negative bacterial infections and MSRA, and the extent of its contribution to AMR in these pathogens is not known.

Other evidence suggests agricultural use of antibiotics can have important negative health impacts in poor countries:

- In developed countries, industrial agriculture is considered to be the most important reservoir for antimicrobial resistant *Salmonella* and *Campylobacter*; an increasingly important reservoir for MRSA; and, an important but not quantified reservoir for *E. coli* and enterococcal infections (EFSA, 2008; WHO, 2011). Industrial agriculture may also be important reservoirs for these pathogens in poor countries.
- In the first attempt to assemble information on national AMR surveillance, the WHO collected data on resistance in infections caused by 9 bacteria of international concern (WHO, 2014). Of these 9, we know that non-typhoidal salmonella is usually acquired from animals or animal products, and *E. coli* and *S. aureus* are sometimes acquired from animals and their products (although LA MRSA is believed to be mainly acquired from contact with animals). The other 6 bacteria of concern are primarily problems of medical use of antibiotics.
- In developed countries, agriculture is the primary user of antimicrobials in terms of total quantities; much agricultural use results in sub-therapeutic exposures for bacteria; drugs of every important clinical class are used; and humans are exposed to resistant pathogens via consumption of animal products, and via widespread release into the environment (Silbergeld et al., 2008). Some of these factors are likely already true for developing countries, and the trends are for developing countries to become more similar to developed countries in these respects.
- Case studies show that drug resistance in human pathogens is associated with animal pathogens in developing countries. For example, samples from gentamicin-resistant urinary tract infections and faecal *E. coli* isolates from humans and food animal sources in China showed that 84% of human samples and 76% of animal

samples contained the same gene for gentamicin resistance (Ho et al., 2010). It is now theorized, from molecular and epidemiological tracking, that the resistance determinants found in salmonella outbreaks (strain DT104) in humans and animals in Europe and the United States likely originated in aquaculture farms of the Far East and the 1992 multiresistant *Vibrio cholerae* epidemic in Latin America was linked to the acquisition of antibiotic-resistant bacteria arising from heavy antibiotic use in the shrimp industry of Ecuador (Marshall & Levy, 2011).

Although it is not possible to quantify the impacts of agriculture associated AMR, they are potentially high. Antimicrobial-resistant infections currently claim at least 50,000 lives each year in Europe and the US (Laxminarayan et al., 2013) and some estimate that drug-resistant infections will cause 10 million extra deaths a year and cost the global economy up to $100 trillion by 2050 (Review on Antimicrobial Resistance, 2014), with most impacts due to *E. coli*, malaria and tuberculosis (of these, only *E. coli* resistance could be linked to agricultural use). **Reliable estimates of the true burden of AMR infections in developing countries do not exist.** In India, nearly 60,000 infants die each year from antibiotic-resistant infections (Laxminarayan et al., 2013). If even a small proportion of these cases are due to agricultural use of antibiotics, the overall health burden would be significant.

The potential health and economic impacts of agriculture linked AMR in developing countries are:

- Human illness from pathogens acquired from direct or indirect contact with animals and their waste or through consumption of animal products.
- Human illness from other pathogens that have acquired copies of a resistance gene from antibiotic resistant bacteria acquired from animals or animal products.
- Animal illness from resistant pathogens. Resistance has developed to virtually all anti-infectious drugs used in agriculture (Grasswitz et al., 2004). But while the impacts of resistance to trypanocidal and anti-parasitic veterinary drugs in developing countries is well documented (Molento et al., 2011), there is less information on the impact of AMR infections on animal health.
- Food products with higher than acceptable antibiotic residues may be rejected. Currently this mainly applies to food exported from developing countries, especially aquaculture products (as regulations governing residues are rarely enforced in domestic markets). For example, antibiotic residues accounted for 28% of EU rejections and 20% of US rejections of aquaculture with Vietnam, China, Thailand, Bangladesh, and Indonesia most affected (UNIDO, 2011).

In developing countries there is a dual problem of overuse and lack of access to veterinary antibiotics. Many more animals die from lack of access to antibiotics than from resistant infections. Meta-reviews of studies from Africa suggest 10% of adult ruminants and 25% of young ruminants die prematurely each year, most from disease (Otte & Chilonda, 2002). Others estimate livestock disease in Africa costs from $9 to $35 billion annually (Grace et al., in press). Reducing agriculture associated AMR requires reducing the quantity and/or improving the quality of antimicrobial use. Interventions aimed at reducing quantity may result in higher losses from treatable diseases and net negative impacts on food security and poverty.

In developing countries there are related challenges of low livestock productivity and lack of animal source foods contributing to 2 billion cases of 'hidden hunger' due to micronutrient deficiencies. Antibiotics reduce feed requirements and increase weight gain by 2-15% (Hao et al., 2014). Because feed is the major cost in industrial systems and profit margins low, stopping antibiotics without putting alternatives in place could seriously affect the ability of intensive systems to provide cheap, abundant animal source foods.

When antimicrobials were banned for growth promotion in Europe, countries saw initial increases in antimicrobials used in animal treatment, but it appears with time and improvements in husbandry most countries saw sustained decrease in antimicrobial use without major impacts in productivity (Marshall & Levy, 2011). An evaluation in Denmark found cost of swine production increased by just 1% after the ban while production declined by just 1.4% (WHO, 2002). Still, it has been argued by some in animal husbandry that the different situation in the United States means antimicrobial restrictions will result in increased morbidity and mortality, projected to cost $1 billion or more over 10 years (Marshall & Levy, 2011). It is difficult to estimate the likely impacts of a ban in developing countries, but they could well be more severe than in Europe. This is because housing, husbandry and biosecurity are often poor in developing countries, the environment is often more suited to pathogen survival and transmission, and pathogens are more common.

Evidence Gaps

- Antimicrobial usage is not well measured in most developing countries, making it difficult to evaluate the relative contributions of veterinary and human antibiotic use on resistance in bacterial populations.
- We do not have systematic, comprehensive data on the prevalence of AMR infections in livestock and fish or the costs of these in terms of reduced productivity and increased treatment costs.
- We do not know the contribution of antimicrobial use in food animals in developing countries to the development of AMR resistance in infections affecting people. This makes it difficult to assess the impact of agriculture-related AMR on human health.
- We do not understand important aspects of transmission of AMR pathogens or genes including the role of animal products, animal contacts, and environmental contamination; direction of transmission; and other related factors such as
- The costs and benefits of antimicrobial use under different systems (intensive, extensive), species (cattle, pigs, poultry, fish) and use scenarios (current, reduced, increased use) are not known. These should include the costs of lack of access to veterinary antibiotics or ability to use in growth promotion.
- While banning non-therapeutic antimicrobials in Europe has had few negative consequences on animal production or welfare, we do not know if this would be the case in for developing countries.

SECTION 5

Technical capacity in developing countries to assess antibiotic use, antibiotic resistance utilising standardised tools in the livestock fisheries sub-sector

Evidence

Regulatory capacity is generally good and most countries have policies and regulations in place to control the use of antimicrobials in livestock and fish. A survey by the OIE found 91% of members has legislation covering veterinary medicines, and in most cases legislation covered importation, distribution, marketing and use. Around half (51%) of countries have banned antimicrobials as growth promoters, while 19% have a partial ban, and 30% no ban. Legislation, surveillance systems and bans on growth promotion are all trending upwards (Diaz, 2013). There is increasing support for integrated “One Health” management of AMR which is articulated in the WHO and OIE strategies (WHO, 2012). However, there appears to be lack of communication on legislation: for example, state veterinary services who are best placed to understand regulation for veterinary drugs report that regulation is in place (OIE, 2012) but WHO offices in the same countries report low or no regulation in place for veterinary drugs (Gelband & Delahoym 2014). Moreover, dysfunctional health systems (human and veterinary) prevent translation of policy and regulation into action.

Surveillance capacity for AMR pathogens in animals, food and agricultural environments in developing countries is generally low. Antimicrobial drug resistance is usually not monitored in under-resourced countries because they lack surveillance networks, laboratory capacity, and appropriate diagnostics (Vernet et al., 2014). In 2014, the WHO reported the first attempt to assemble information on national AMR surveillance; however, this did not include data on animals, animal products or agricultural environments. A survey of African chief veterinary officers (Grace et al., in press) found 66% had no information on AMR in animals, 21% considered it was occasional, 4% common and 9% not present in their country. Even for surveillance of AMR in humans capacity, in most developing countries is low. Moreover, the lack of agreed global standards for AMR surveillance, and discrepancies in performance and interpretation of laboratory findings can be such that bacteria considered resistant in one laboratory could be classified as susceptible if tested in another laboratory.

Surveillance capacity for antibiotic use in agriculture is low but there are plans to improve reporting. Most developing countries have limited capacity for surveillance of antibiotic use in agriculture (Rushton, 2014). Moves are underway to improve this. A study by the OIE found that only 27% of members had an official system for collecting quantitative data on veterinary medicines, and of those that did around half made the information available (Diaz, 2013). Nearly all of these were developed countries. A survey of African chief veterinary officers (Grace et al., in press) found just 7 out of 34 respondents (and 54 countries sent questionnaires) were able to provide quantitative information on use of antibiotics in livestock and fish. The OIE is considering how to improve reporting on veterinary anti-microbial use, with an initiative to be launched in 2015.

Most countries have limited laboratory capacity. In Africa, a recent report found challenges including: lack of external quality assurance; lack of essential reagents; inadequate standard operating procedures; noncompliance with internationally recognized standards; insufficient capacity for data analysis and dissemination; inadequate training of staff performing and interpreting susceptibility tests; lack of national guidelines on antimicrobial use; and, weakness of national programs for AMR (WHO, 2013). Similar challenges are found in Asia; for example, in Vietnam, data ownership, data quality and permissions were flagged up as especial challenges (Wertheim et al., 2013). A common problem is that laboratories deal with only human or animal samples.

The capacity to monitor and control sale of veterinary drugs is very weak in most countries. A key element of most veterinary medicine legislation requires that antimicrobials are used only if prescribed by a veterinary professional. However, most (in some cases nearly all) antimicrobials in developing countries are applied without veterinary oversight (Grace et al., 2009). Moreover, the high numbers of animals, few veterinarians and the non-viability of private veterinary practice in many countries imply a prescription-only system with direct veterinary oversight is not feasible in the foreseeable future. Even when veterinary oversight is present, veterinarians may not have sufficient information or incentives to ensure that drug use is rational.

The problem of veterinary drug control needs to be assessed in the context of control of medical drugs. In many developing countries, human antibiotic use is relatively uncontrolled, and most community care is provided by the informal sector (Bloom et al., 2011). Commonly used antimicrobials are comparatively inexpensive (often costing 10- to 30-fold less than the same drugs in industrialised nations). In addition, western pharmaceutical companies have been reported to distribute antibiotics that are no longer effective or not approved in Europe or North America to developing nations (Davies & Davies, 2010). Most low and middle income countries report poor enforcement of antibiotic use policy and when human drugs cannot be well controlled, it is unlikely that veterinary drugs will be.

The capacity to monitor and control the use of veterinary drugs is also weak. A literature review of vet drug use in developing countries (annex 1) shows: drugs are widely used by intensive farmers and less so by smallholders; vaccines and preventative treatments are under-used; and, that drug use is often irrational due to lack of proper diagnosis or information on correct treatments. To give two examples: in one commune in Vietnam, 100% of the large-scale farmers and 60% of small-scale farmers made diagnoses and treatments and 60% of them made treatments themselves (using 45 antibiotics readily available from agricultural input suppliers. In another example from West Africa, farmers reported that 25% of cattle fall sick each year with trypanosomosis and that 90% of sick animals were treated, mostly by farmers. Diagnosis and dosage were reasonably accurate but 15% of observed treatments were under-dosed (Grace et al., 2009). New approaches are needed to improve the performance of human and animal health markets, particularly in meeting the needs of the poor. This cannot be achieved by simply importing regulatory frameworks and approaches from the advanced market economies (Bloom et al., 2011).

Evidence Gaps

- The lack of comprehensive, systematic, repeated, integrated surveillance systems for AMR that cover hospitals, communities, animals, food products and agro-food environments is a major gap that will be difficult to fill.
- The lack of quantified information on veterinary and medical drug use is a major gap, as this would allow a rapid screening for countries most at risk for agriculture-related AMR. In many countries this information could be easily obtained as antimicrobials are imported.

- The lack of laboratory capacity is a long-standing problem in developing countries. Much effort and expense has been spent on improving capacity, and best approaches exist.
- The lack of harmonised approaches for assessing and reporting AMR is an important gap, which would not be difficult to address in countries where AMR is actively underway.
- Given these global coordination issues, there is a role for a binding international legal framework to encompass the issues of drug access, conservation and innovation.
- The weak ability to control the sale and use of human and veterinary antimicrobials in developing (and some developed countries) is a major gap that will be difficult to overcome.

SECTION 6

Key drivers of antimicrobial resistance in livestock and fisheries production in the developing world

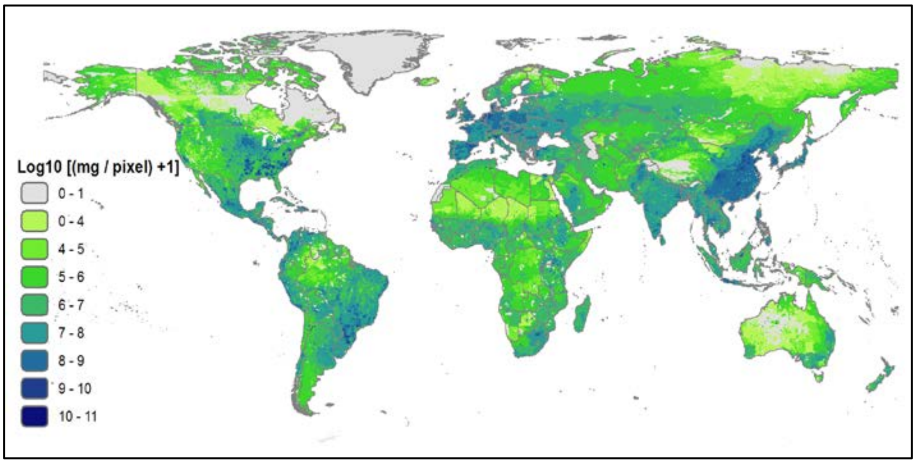
Evidence

The key driver of agriculture-related AMR is the quantity and quality of use of antimicrobials in livestock production and aquaculture. The key driver of antimicrobial use is profitability. While small amounts of antibiotics are used in crop cultivation and forestry, and for treating companion and work animals, in developing countries most non-medical use of antimicrobials is almost certainly in livestock and farmed fish production. Moreover, it is likely that most veterinary use is in intensive production rather than pastoralist or smallholder systems. Antimicrobials are used because they save money by treating and preventing disease and by promoting growth. We don't have accurate information on antibiotic use in developing countries but several hundred thousand tons are probably used, and in many countries agricultural use probably exceeds medical use (Annex 2).

The underlying driver for antimicrobial use and development of AMR is the livestock and aquaculture revolutions: China, Brazil and India are hotspots. This in turn is driven by population increases, urbanisation, improving economic conditions and globalisation. Based on livestock intensification, China, Brazil and India are current hotspots, and future hotspots with fastest growth of the intensive livestock sector in Myanmar, Indonesia, Nigeria, Peru and Vietnam (Van Boeckel et al. 2015). This estimated:

- Total consumption in the livestock sector in 2010 was 63,151 tons
- Global antimicrobial consumption will rise by 67% by 2030 to 105,596 tons
- The greatest increase (doubling) will be in the BRICS (Brazil, Russia, India, China and South Africa)
- China's livestock industry by itself could soon be consuming almost one third of world's available antibiotics

Figure 1 Global antimicrobial use in food animals (mg per 10km pixel)



from Van Boeckel et al., 2015

In terms of quantity, **intensive swine and cattle production are the most important users** and poultry and fish are apparently minor (<10% each of total use) (MR, 2014). However, these estimates are based on market reports, which, although global, are probably more representative of developed countries (Annex 3). Indeed, OECD data suggests poultry use may be more important than market reports suggest (Grave, 2010). Although the total quantities of antibiotics employed in aquaculture are estimated to be smaller than those used in land animal husbandry, there is much greater use of antibiotic families that are also used in human medicine (Marshall & Levy, 2011). Extensive and smallholder production appear to use relatively small amounts of antibiotics, and most is used for treating sick animals rather than disease prevention or growth promotion. Intensive production often operates on narrow margins, so the savings from use of antibiotics are important for profitability. Moreover, intensive systems require more antibiotics as animals are kept in high numbers and density. Most organic production requires that antibiotics should not be used.

Quantities of antimicrobials used reflect by size, intensification, and governance of the livestock and fish sector: China, India, Vietnam, Thailand, Brazil, Mexico and Indonesia may be hotspots. China is the world's biggest poultry meat, egg and pork producer. Brazil, India, Mexico and South Africa are important developing country poultry producers and Brazil, Mexico, Vietnam and Indonesia important pork producers. In Latin America, >90% of pork and poultry is produced intensively, in E Asia 70-80%, in SE Asia 50-60%, in Africa 40% in S Asia, 20% (Herrero et al., 2013). Thailand has an unusually high level of intensive production and of antimicrobial use in agriculture. Most (86%) global aquaculture is in Asia with 62% in China. Antibiotics are said not to be used widely in the low-density fish farming in lakes and reservoirs that predominates, but are a problem in production of high value shrimp, eel and turtle (Jiang, 2000). Chile is the second largest producer of farmed salmon and the only important developing country producer. It uses around 300 tons of antibiotics: in contrast, the largest salmon producer, Norway, uses less than 1 ton (relying instead on vaccination and husbandry measures to control diseases) (Annex 2). Other developing countries with important aquaculture sectors are India, Viet Nam, Indonesia, Bangladesh, Egypt, Myanmar, Philippines and Brazil. Antibiotic residues are a common problem with fish products exported from Vietnam, China, Thailand Bangladesh, and Indonesia most affected (UNIDO, 2011). Anecdotally, livestock sector governance is low in most of Asia and most of sub Saharan Africa and somewhat higher in South Africa and Latin America.

The quality of antimicrobial use is also important:

- Not using the antimicrobials most essential for human health in agriculture (critically important list) would slow resistance to these antimicrobials.
- Using antimicrobials that are also used in human medicine for growth promotion is especially conducive to AMR because exposure of many animals to low dosages makes resistance more likely to emerge.
- The practices of treating all animals in a group if one falls ill (metaphylaxis) and of treating animals when they are exposed to conditions that make them likely to fall ill (prophylaxis) increases the amount of antimicrobials used and as such would encourage resistance. However, if only treating sick animals results in more serious and frequent illnesses, prophylaxis and metaphylaxis may reduce the total amount of antimicrobial used.

Enabling factors
While quantity and quality of antimicrobial use in agriculture are the proximate drivers of agriculture related AMR, there are other factors, which influence development of AMR. These include:

- **Lack of awareness and concern over antibiotic use:** Despite heightened awareness in high-income countries and recognition that antibiotic resistance is a global problem, the issue is still not on the agenda for most low-income countries and some middle-income countries For example, a donor report of major health accomplishments in recent years, "resistance" figures prominently in discussions of malaria and tuberculosis but is not mentioned at all in relation to common bacterial infections (Gelband & Delahoy, 2014). A review of research on AMR enteric bacteria in east Africa, reported that research progress on AMR was slow despite the importance of antibiotic purchase in health budgets. Moreover, just 24% of studies focused on animal or animal product AMR (Omulo et al., 2015). Many veterinarians and others involved in food production do not believe that antimicrobial use in animals has extensive negative health impacts in people (McEwen, 2001).
- **Lack of information:** Developing countries lack information on the presence and prevalence of AMR in animals and their products and of the health impacts and cost of AMR illness in people and animals.
- **Fake and substandard drugs:** There is much concern over counterfeit[3] and substandard drugs in animal health care, but insufficient data to understand its importance. Some counterfeits contain no active ingredients, and these will not lead to drug resistance (although they will lead to treatment failure). Counterfeits and substandard products, which contain active ingredient at a lower level, will increase the chance of resistance developing. There is no comprehensive information on fake/substandard veterinary drugs. According to IFAH estimates, the value of the official market for veterinary drugs in Africa runs around $400 million a year and the trade in sub-standard and non-registered drugs is just as large. Others consider that parts of the pharmaceutical industry have incentives to over-emphasize the problem of fake and substandard drugs in order to increase markets for their products. Farmers frequently complain that products are ineffective, when the problem is actually resistant pathogens, misdiagnosis or under-dosage (Grace, 2009). Few empirical studies have been carried out and these have mixed results, some finding that drugs thought to be substandard were effective (Asmare et al., 2005; Chaka et al., 2009); others that drugs had much less than the specified amount of active

[3] WHO defines spurious/falsely-labeled/falsified/counterfeit (SFFC) medicines as medicines that are deliberately and fraudulently mislabeled with respect to identity and/or source while substandard medicines are pharmaceutical products that do not meet their quality standards and specifications as a result of negligence, error or counterfeiting.

ingredients (Grasswitz et al., 2004). Even in human medicine, data is insufficient to estimate the extent of the problem or its impact on human health, although an often-quoted estimate is 10% of the global supply is counterfeit (Newton et al., 2010).

- **Poor integration between human and animal health sectors**: At international level, there is good collaboration between WHO, OIE and FAO in the area of AMR. However, in developing countries (and many developed) data on antibiotic use in human health care and in agriculture are not systematically collected or shared.
- **Lack of alternatives to antibiotic use:** European countries were able to impose a ban on the use of growth promoters without excessive negative impact on productivity, profitability, animal health or welfare. The feed industry developed alternative growth promoters and good practices were adopted to ensure healthy herds and flocks. This level of resilience to such bans may not exist among farmers in developing countries where such a ban could lead to the use of (poor quality) antimicrobials obtained on the black market – exacerbating the problem – or else (or as well as) a considerable increase in disease, with consequent mortality and morbidity losses.

Evidence Gaps

- We don't have good information on the current production losses in animal agriculture caused by disease and the extent to which these could be averted through better use of antimicrobials or their alternatives.
- Alternatives to using antimicrobials for growth promotion have been successful in Europe but their practicability and affordability in developing countries are not well understood.
- There have been considerable investments in disease control options such as vaccines, vector control and resistant breeds in developing countries but these have not been evaluated from a perspective of reducing veterinary drug use.
- The prevalence and composition of substandard and counterfeit drugs is not well known nor the impacts on treatment failure and fostering resistance.
- The level of resilience of livestock farmers in developing countries to bans or restricted access to antimicrobials.
- We know policy and regulation alone is unlikely to improve use of vet drugs but the options for improving the use of vet drugs in agriculture and their effectiveness, feasibility and affordability are not well understood.

SECTION 7

Modalities of reducing antibiotic use and levels of resistance

Evidence
There is broad consensus on what is required to manage AMR in human and animal health. These include:

- Reduce need for antibiotics by improving public and animal health (immunization, infection control, sanitation, housing and environment).
- Change incentives for prescribing antibiotics and sales made without a prescription.
- Change incentives to speed the discovery of new antimicrobials.
- Reduce environmental contamination with antibiotics from agricultural, hospital and community use and manufacture.
- Develop global, integrated policies covering the use of antibiotics.
- Phase out antibiotic use for growth promotion and non-therapeutic use in agriculture.

Rational drug use
A wide range of interventions using educational, managerial, regulatory and economic approaches to improve drug use has been studied in human health and much has been learned about success factors (Aranda & Mazzotti, 2013). For example, the OIE and veterinary professional societies have developed guidelines on judicious veterinary drug use and Denmark has put significant limits on the ability of veterinarians to profit from the sale of antimicrobials in food production (McEwen, 2001). In developing countries, most animal antimicrobial use is probably without veterinary oversight and there are additional challenges to improving use. However, approaches shown to improve drug use by informal providers would be relevant. A review of 70 interventions found that training was the most common approach but was relatively ineffective. However, if combined with strategies to change market conditions (by changing incentives and accountability environment) better success was achieved (Shah et al., 2010).

Governance of antimicrobial use
There is consensus that antimicrobial use requires oversight, and that medical and veterinary use needs to be considered holistically. Tools for improving governance include lists of critical drugs for human and veterinary use, prescription requirements and guidelines (e.g. stopping medically important antibiotics in agriculture, cascade systems, guidelines for off-label use), and guidelines for monitoring antimicrobial use and AMR. So far, there has been little success implementing these in livestock and fish production in developing countries (but also relatively little investments in implementing these).

The OIE sees empowerment of veterinarians and restriction of antimicrobial prescription to the veterinary profession as key to better governance of veterinary antimicrobials. However, private veterinary practice has not been able to establish or provide services on significant scale in most developing countries. Private vets are usually too costly for smallholders, and intensive industrial agriculture firms often prefer to employ veterinarians directly, which makes them less independent. Recent models based on franchises may be more viable but are still under evaluation (http://www.farmafrica.org/kenya/sidai). 'Agro-vets', that is small shops run by 6 month – 2 year trained professionals have been successful but are not in line with current OIE policy (Lewis, 2001). Community animal health workers have proven very effective (Leyland et al., 2014), and may be politically acceptable, but can be expensive to train and oversee. Public veterinary services often lack resources to support CAHWs while private veterinarians often oppose them as actual or potential competitors. All these private veterinary models are prone to perverse incentives as practitioners' earnings are tied to dispensing. Only one study has investigated rational drug use by farmers: this found farmers in west Africa were mainly responsible for buying and using antibiotics and that providing simple information on correct drug use could improve use and reduce the proportion of under-dosages, which is an important driver for AMR emergence (Grace et al., 2008).

Alternatives to antimicrobials in animal agriculture
European countries stopped use of medically important antibiotics and growth promoters in agriculture. This was followed by a widespread change in farming practices and a reduction in AMR in bacteria important to human health being found in farm animals. This natural experiment showed routine antibiotics are not necessary to produce healthy animals, provided their living conditions, rearing and foods are improved and curative antibiotics are used for clinical illness. However, production without routine antibiotics can increase costs and management efforts. On the other hand, these management efforts often lead to better housing conditions and improved animal welfare. A caveat is that the benefits of antimicrobials for growth promotion seem higher under poor hygiene conditions (McEwen, 2001). These are characteristic of intensive livestock production in developing countries, and consequently will increase the difficulty of developing country producers from shifting away from reliance on non-therapeutic antimicrobials.

Nonetheless, there are many promising innovations, which could support profitable and productive agriculture with less use of antimicrobials. These include:

- Non antibiotic growth promoters such as In feed enzymes, competitive exclusion products and probiotics/prebiotics
- Other animal health technologies, such as vaccines, vector control, phages, and disinfectants – many of which are underused in developing countries
- Diagnostics to improve drug selection and identify AMR pathogens
- Management and biosecurity innovations such as all-in-all-out systems, pathogen free systems, reducing stocking density and improving waste management
- Genetically disease resistant animals and avoidance of monocultures of genetically similar animals.

Some of these interventions may also improve animal welfare (e.g. reducing stocking density) and reduce environmental externalities of animal agriculture. More radical suggestions are to decrease the amount of animal source food consumed or shift from intensive to extensive or organic animal production.

Dual problem of overuse and lack of access
In rich countries, underuse of antibiotics and consequently a reduction of preventable deaths from infection in livestock have been greatly reduced. In poor countries, many more animals die from lack of access to antibiotics than from resistant infections. In addition, the OIE estimates that 25% of livestock production is lost due to disease globally (OIE, 2015). This represents at least 60 million tonnes of meat and 150 million tonnes of milk with a value of approximately USD 300 billion per year**.** In this context, measures to restrict the use of antibiotics in agriculture could have un-intended consequences on Income derived from livestock, livelihoods and nutrition.

Evidence Gaps

- Tackling agriculture linked AMR: While the principles of managing AMR are well accepted, there is very little evidence on how this can be practically achieved in the context of developing country agriculture.
- Rational drug use: There has been very little research into better management of veterinary antimicrobial use, but some of the lessons learned from medical interventions probably apply.
- Animal health service delivery is sub-optimal in most developing countries and new approaches need to be developed and evaluated.
- There are many promising innovations which could support profitable and productive agriculture with less use of antimicrobials but further development and adaptation is needed before they can be expected to adequately substitute for current uses of antibiotics in animal agriculture in developing countries.

SECTION 8

Recommended research priorities

A number of recent reviews clearly show that use of antibiotics in food animals (particularly nontherapeutic use) can affect the health of people on farms and, via the food chain, the health of consumers and communities. Evaluations following the bans in Europe on nontherapeutic use of antimicrobials show bans are feasible and affordable, at least, in the European context. **However, the contribution of agricultural antimicrobial use to the overall burden of human AMR infections and the health benefits of bans on AMR in humans are less clear**. AMR to human pathogens has overall continued to increase despite the bans.

Moreover, in developing countries, there is a dearth of evidence on most aspects of agricultural related AMR. This includes; the use of antimicrobials in agriculture, the impacts of this use on human and animal health, the acceptability and feasibility of stricter control on antibiotic use in agriculture, and the costs and benefits of stricter control. The latter should take into account trades offs between overuse and lack of access to antimicrobial drugs, and between the health impacts of AMR attributable to antibiotic use and nutritional problems attributable to insufficient intake of animal source foods. Given the current failure to control human and veterinary drugs, it is likely that bans would be difficult to implement. And given the problems of lack of access to veterinary drugs and insufficient intake of animal source foods, it is possible that restricting the use of veterinary drugs could have additional negative impacts, unique to developing countries.

At the same time, AMR is intrinsically a global problem that can only be managed at supra-national scale and by addressing all of the important uses of antimicrobials. The current strong momentum to take action on AMR provides an opportunity to address the problem globally and comprehensively, addressing medical and veterinary use. This should be done in an evidence-based way which includes filling knowledge gaps, careful piloting of interventions, and rigorous evaluation of success and failure. In this context, some of the key research questions for better managing agricultural use of antimicrobials in developing countries, based on this report, but also the literature, are:

How big a problem?

- What is the current evidence on agricultural AMR in developing countries in terms of prevalence, trends, and variation by farming system, species and country?
- How much antimicrobials are used in agriculture (absolutely and relatively to medical use) and how does this vary by species, system and country?
- What is the contribution of antimicrobial use in food animals in developing countries to the development of AMR resistance in infections affecting people?

How is it created?

- To what degree and in what directions are there transfer of antimicrobial resistance (i.e. between plants, animals, humans and environmental organisms)? What are the risk factors for transmission?

- What is the rate of development of medically important bacterial resistance in food-producing animals, in relation to duration of exposure to and concentration of antimicrobial and including the resistance selection potential of antimicrobials permitted minimum residue levels?
- What is the effect of current food processing and distribution on the emergence and spread of AMR?
- What is the effect of environmental contamination with antimicrobials from veterinary, medical and agronomy use and manufacture on the emergence and spread of AMR?
- How common are fake and counterfeit veterinary drugs, and what is their contribution to the development of AMR?
- What are the incentives for producers to use antimicrobials and how do animal health systems restrict or increase access to veterinary drugs?

What should be done about it?

- What are the costs and benefits of antimicrobial use under different systems (intensive, extensive), species (cattle, pigs, poultry, fish) and use scenarios (current, reduced, increased use)? These should include the costs of lack of access to veterinary antibiotics and inability to use in growth promotion.
- What is the effect of cessation of use of antimicrobials on the prevalence and persistence of resistant bacterial in food-producing animals and their immediate environment?
- Given the lack of firm information on many aspects of antimicrobial use in developing country agriculture and its health impacts, but the strong possibility this could cause irreversible harm, what actions are appropriate and which require further evidence?

What are promising approaches for managing agricultural related AMR?

- How can comprehensive, systematic, repeated, integrated surveillance systems for AMR that cover hospitals, communities, animals, food products and agro-food environments be developed?
- What are the threshold levels of resistance that are of public health concern? How can these be monitored and what are the actions when thresholds are exceeded?
- What new approaches to animal health service delivery can address the dual burdens of lack of antimicrobial access and antimicrobial over use?
- What animal health and husbandry innovations would support profitable and productive agriculture with less use of antimicrobials and how can these be extended to developing countries?
- How can the management and technology innovations that support animal production without use of growth promoters in Europe be extended to developing countries?
- What is the potential role of consumer demand, high value markets and private standards in reducing antimicrobial use in developing country agriculture?
- How can rational drug use principles be extended to agricultural use of antibiotics in developing countries?

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Annex 1 Literature review on veterinary drug use in developing countries

Selection of keywords used: veterinary drug use ('in Africa' and 'in Asia'); rational drug use; knowledge attitude practices and ('specific disease'); improper use of veterinary drugs

Databases searched: Google Scholar, PubMed

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
Addah et al (2009)	Ghana Sample size n=100 70 farmers and 30 herdsman	Ticks and helminths	Acarides use (submitted by participants for inspection): …66% used Cyprin …10% used Hexiprametrin …6% used Amitraz …5% used Deadly backline …3% used herbal preparations …10% used unorthodox chemicals 52% of respondents used acaricides at levels below recommended dosages Administration of acarides …80% on-the-spot hand dressing …15% dipping/washing …5% pour-on Antihelminthics use (submitted by participants for inspection): …7% used Albendazole (2.5 w/v) …16% used Albendazole (25mg) …11% used Albenol (2.5%) …15% used Albevet (10%) …15% used Analgon (25mg) …30% used BenvetGR (2500mg) …16% used Albenol (25mg) 72% of respondents used antihelminthics at levels below recommended dosages Administration (who) of both drugs …50% pastoral herdsman (I think this could mean self-administered) …30% livestock farmers (I think this could mean self-administered) …11% community livestock workers …9% veterinary personnel By label examination of both drugs …75% of acaricides used by participants had not exceeded the expiry date …53% of antihelminthics used by participants had not exceeded expiry date	More on their methods: "Livestock farmers submitted acaricides and anthelminthes (in their original containers) used for treating their animals for inspection. Info from drug labels was documented: trade name, country of origin, manufacturer, active ingredients, expiry date, language of instruction/ inscription, recommended dosage, mode of administration and official certifying agency. The containers used to measure each parasiticide and water for dilution when indicated, were also used to determine whether the product was used as recommended on the label, over-dosed or under-dosed. In some instances, respondents were asked to demonstrate how they used either parasiticide. Tick and helminths control practices of farmers were also observed during

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
			Source of both drugs …41% from private veterinary shops …32% from village markets …25% from district MoFA vet clinics …2% chemical peddlers	visits."
Bardosh et al (2013)	Uganda Sample size n=495 livestock keepers	Trypanosomosis (AAT)	Types of drugs used: …35% - pyrethroids …25% - amitraz …40% - could not name product Of those who used acaricides …21% claimed to spray for both ticks and tsetse flies …79% sprayed only for ticks "This was explained by the low tsetse challenge in the area, beliefs about disease risk (that acquiring human sleeping sickness was unlikely), the higher cost of pyrethroids and a belief that acaricides could only kill tsetse flies if the fly came into direct contact with the insecticide during spraying." 17% did not use acaricides at all In the rainy season, cattle were sprayed …15.7% weekly …21.5% fortnightly …2.8% every 3 weeks …24.5% every month …18.7% irregular intervals	"Interviews and focus groups showed that adhering to a prescribed spraying interval was a challenge for farmers due to competing interests and demands on time and money. Tick presence rather than a prescribed time period dictated the spraying interval."
Catley et al (2002)	Kenya	Bovine trypanosomosis	No % listed, only ranking "Herders used an integrated approach to control bovine trypanosomosis involving up to 10 control methods" Modern methods listed by informants for controlling bovine trypanosomosis (rank order): …Trypanocides …Pour ons …Dips Indigenous methods listed by informants for controlling bovine trypanosomosis: …movement of cattle away from tsetse-infested areas …bush clearance to reduce contact with tsetse …dung fires in kraals …blood letting …herbal remedies	
Ezenduka	Nigeria –	Poultry	Most commonly used antibiotics	From the

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
et al (2011)	Enugu State n=25 layer farmers	diseases	…100% oxytetracycline …72% macrolides …52% aminoglycosides …12% quinolones …8% sulphonamides …8% nitrofurans …(no%) beta-lactams and ionophores are least used	conclusion, but no supporting data that I could find reported in article: “It is also very obvious that poultry farmers (without the consultations of a Veterinarian) in the study area do not adhere to withdrawal periods of antimicrobial drugs; most times, farmers do not even bother reading the manufacturer’s instructions before the use of a drug.”
Grace et al (2009)	Burkina Faso, Mali and Guinea n=895 farmers	Cattle trypanoso mosis (AAT)	An average of 3.5 preventive strategies per farmer were used, across all three countries Treatment “Most frequently cited drug of first choice for AAT treatment was DIM and followed by ISMM. Most popular drug of second choice (or fallback) was ISMM.” …89.6% of farmers used trypanocides to treat cattle they believe are sick with AAT, either as sole treatment or alongside non-trypanocidal modern drugs …5.4% used non-trypanocidal drugs only Treatment (who) …41.8% of cases of sick cattle were treated by community members other than the owner or herder …31.1% of cases were treated by the farmer or his herder …13.9% of cases were treated by vets Preventive methods …49.7% used trypanocidal drugs, either ISMM or repeated doses of DIM during risk periods …32.5% avoided high-risk areas by watering cattle at pumps instead of water-courses and grazing in areas where flies are fewer …7.4% kept trypanotolerant cattle	

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
			<1% of farmers reported unsafe practices such as giving ISMM and DIM at the same time or mixing trypanocides with antibiotics and giving as injections.	
Heffernan et al (2011)	India n=601 (414 urban and 187 peri-urban/rural livestock keepers)	Vaccines, in general	Vaccination behavior (n=184) …47% foot-and-mouth disease (cattle/buffalo) …21% hemorrhagic septicaemia (buffalo) …14% fowl pox (chicken) …17% Newcastle disease (chicken) …0.5% rabies (horse) …0.5% tetanus (goat) …1% typhoid (chicken) 43% of farmers reported having vaccinated any of their animals during the past 12 months. Only 30% of these farmers named a livestock disease for which a vaccine exists, i.e. Hemorrhagic Septicaemia (HS), Foot and Mouth Disease (FMD), Newcastle disease (NCD), Rabies, Tetanus, Fowl Pox and Fowl Cholera. "Vaccination was often confused with treatment for other diseases such as bloat or intestinal parasites…Urban producers had the highest level of nonreporting."	From the conclusion, "Among participants, the adoption of livestock vaccination was, on a macro-level, deeply embedded within the existing social system and on a more micro-level, related to very specific knowledge frames. Contrary to conventional wisdom, the 'ability to pay' for vaccination, did not appear to be the primary inhibitor to effective vaccination coverage."
Kisinza et al (2011)	Tanzania Interviews with agriculture and public health officers, total number of interviews was not reported	Malaria among cattle and poultry	*No percentages, just lists* Insecticides used for livestock spraying: …Stelladone (Chlorfenvinphos 300g/L) …Dominex (Alphacypermethrin 10%) …Ectomin (Cypermethrin) …Sevin dust (Cabaryl 75g/Kg). Others included Tactic, Triatix, Norotrax and Amitix all of which contain Amitraz 12.5%, for cattle only. Dipping or spraying of animals was reportedly done 2 to 4 times a month.	
Liebenehm et al (2011)	Mali and Burkina Faso Results from an impact evaluation of program	AAT	Practices of farmers – program participants …55.92% administer drug by themselves …71.09% use DIM as the first choice …2.37% correctly dose DIM …5.69% correctly dilute DIM …10.9% use ISMM as the first choice …4.27% correctly dose ISMM …11.37% correctly dilute ISMM	From the conclusion, four key elements were identified for enhancing the adoption of RDU principles by farmers: 1. Create

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
	introducing RDU principles to smallholder farmers		…74.41% correctly identify the injection site …65.4% purchase trypanocides at formal market Practices of farmers – non-participants …39.39% administer drug by themselves …73.42% use DIM as the first choice …1.68%correctly dose DIM …1.35% correctly dilute DIM …8.42% use ISMM as the first choice …0.34% correctly dose ISMM …2.02% correctly dilute ISMM …68.35% correctly identify the injection site …45.12% purchase trypanocides at formal market	'knowledge champions' through training, who can be used as mediators in village networks given the right incentive scheme. 2. Improving farmers' veterinary knowledge leads to productivity increase 3. Mass media are effective tools to create awareness, and to transmit knowledge. 4. Boundary spanning approaches between farmers and researchers such as participatory methods increase acceptance
Majekodunmi et al (2010)	Nigeria – Jos plateau Sample size n=30 villages	Trypanosomosis (AAT)	(all based on % of villages, not households as far as I could tell) Trypanocides used for treatment: …50% diminazine only …3.3% isometamidium only …3.3% mixture of diminazine and isometamidium …36.7% used both drugs …6.7% did not know names of drugs Preparation: …43.3% diluted using bottled/packaged water …26.6% used well/stream water …23.2% used water from both types of sources …46.7% water from natural sources was boiled before use …33.3% used the correct amt of water per sachet of drug Point of purchase for drugs, % of villages: …66.7% Agro-vet …3.3% Vet …3.3% Nat'l Vet Research Institute …23.3% Both vets and agro-vets …3.3% Both NVRI and agro-vets (3.3%) Most farmers treated animals	Why curative treatment was preferred to prevention? - Most effective way to control trypanosomiasis (73.3%) - Easiest (13.3); - Only available strategy (10.0); - Cheapest (3.3.)

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
			themselves and all dosed animals incorrectly.	
Moyo & Masika (2009)	South Africa – Eastern Cape Province Sample size n=59 cattle farming households	Tick-borne diseases Most commonly reported ones in the study area: anaplasmosis (89.9%), babesiosis (55.9%) and ehrlichiosis (16.9%)	In the study area, "the gov't provides a dipping service where acaricide Triatix 500 TR (Amitraz 50%) is provided for use in communal dip tanks, once a week in summer and fortnightly during winter. The community selects one member of the community to mix the acaricide in the dip tank. Dipping of cattle is not compulsory and small ruminants like goats are not dipped." 95% of farmers claimed the acaricide (dip wash) was not effective in killing ticks. As a result, …30.5% relied only on gov't dipping service …23.0% complemented the dipping service by buying own acaricides …45.8% used alternative methods (ethno-vet practices) Of those who used commercial acaricides: …22% applied Triatix 125 (Amitraz 12.5%) when spraying …1.7% used pouricides	
Nonga et al (2009)	Tanzania n=20 smallscale broiler chicken farmers	Poultry diseases Most commonly reported diseases which necessitated use of antibiotics (in order from most to least reported): -Coccidiosis -Infectious coryza -Fowl typhoid -Yolk sac infection -Newcastle disease -Gumboro -Helminths	Common antimicrobials used in broiler chickens as reported by farmers (frequency of use - %) …90% Tetracycline (CTC & OTC) …85% Amprolium …85% Sulphonamides …55% Trimethoprim …25% Neomycin …15% Flumequine 90% reported frequent use of antibiotics 75% reported use of antibiotics for treatment and prevention of diseases 65% reported use of antibiotics as a growth promoter 25% reported use of antibiotics as a treatment for chickens when sick	

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
Olatoye and Basiru 2013	Nigeria n=20 farmers	Antibiotics in aquaculture production	90% engaged in routine administration of antibiotics to prevent fish diseases 65% administered drugs routinely to prevent disease outbreak or mortality losses without engaging the services of a vet for disease diagnosis or treatment 100% administered several antibiotics ranging from oxytetracycline, procaine, penicillin G, Malachite Green and enrofloxacin to their fish for disease prevention, treatment, and productivity performance 73% administered oxytetracycline both to the fish stocks and to the fish feed 85.5% were neither aware of the withdrawal period for antibiotics nor the potential hazards of antibiotic residue in humans	From the discussion: "Most of the drugs used by the aquaculture farmers interviewed were not specifically indicated for fish, extra-label use of mostly poultry and human antibiotic preparations was observed to be commonly practiced…This study revealed that most farmers in Ibadan have low level of education and have unrestricted access to antibiotics (over the counter), thereby engaging in self-medication of their stocks as a routine practice without proper diagnosis and not observing of withdrawal period. High proportions (75%) of the respondents in this study were not knowledgeable on the deposition and the public health implication of the residues in fish meat."
Oluwole et al (2012)	Nigeria - Ibadan Sample size n=84 farmers --66 commercial, 9 breeder stock, and 9 mixed stock	Newcastle disease Avian Influenza	Vaccinate against ND: 100% Vaccinate against AI: 16.7% For NDV, 38.1% of farmers complied w/vaccination schedule provided by hatchery source of their chickens; 51.2% vaccinated their birds at strictly 4-6 wks interval and would not use hatchery schedule; 10.7% used partly hatchery schedule strictly combined w/lab advice to vaccinate at variable intervals	
Omeiza et	Nigeria	Poultry	Chloramphenicol (CAP) use	

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
al (2012)	 n=105 poultry farmers	diseases	…20% administered the veterinary CAP preparation …14.3% administered the human CAP preparation to poultry Administration (who) …11.4% reported CAP was administered by vet or paravet …36.2% reported CAP was administered by untrained personnel Administration (mode) …13.3% reported the mode of administration was vet prescription …18.1% reported the mode of administration was manufacturer's prescription …37.1% reported the mod of administration was self	
Peters et al (2012)	Kenya – Kakamega and Machakos Sample size n=558 farmers	Cattle diseases, general	*Did not report % overall, only disaggregated by location* In Kakamega 67% used vaccines to prevent diseases in cattle …28.1% to prevent ECF …17.5% to prevent Blackquarter …7.5% to prevent FMD …6.2% to prevent lumpy skin disease …5.5% to prevent RVF …4.8% to prevent anthrax In Machakos 69.0% used vaccines to prevent diseases in cattle …13.4% to prevent ECF …10% to prevent Blackquarter …12.4% to prevent FMD …8.6% to prevent lumpy skin disease …5.3% to prevent RVF …20.1% to prevent anthrax Detail beyond % of farmers who had treated for these diseases was not specified so vaccine use is all that is reported here in the lit review.	Veterinarians (not specified whether this was private or gov't based) were the most commonly reported person vaccinating cattle (72% in Kakamega and 86% in Machakos) and tended to be organized by the gov't and compulsory when disease outbreaks occurred.
		Diseases in small ruminants, general	In Kakamega …23% used vaccines to prevent diseases in small ruminants …24% used vaccines to prevent CCPP In Machakos …46% used vaccines to prevent diseases in small ruminants …51% used vaccines to prevent	Veterinarians were the most commonly reported person vaccinating small ruminants, but about 25% of farmers reported administrating disease treatments

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
			CCPP	
		Diseases in chickens, general	39.3% used vaccines to prevent diseases in chickens in Kakamega 17.5% used vaccines to prevent diseases in chickens in Machakos	In Kakamega, the paravet was the most common administrator (37.1%) followed by farmer (26.5), then vet (14.6). In Machakos, it was the farmer (25.6), followed by vet (24.4), then paravet (6.7)
Saddiqi et al (2012)	Pakistan Key respondent interviews with key respondents: vet officers (n=15) vet assistants (n=51) traditional practitioners (n=24) small and large scale sheep/goat farmers (n=60)	Gastrointestinal worms in sheep and goats	Use …76% used modern anthelmintics …20% used a mix of both traditional and modern …4% used traditional anthelmintics …50% of traditional practitioners used both modern and traditional anthelmintics Preferences …58% preferred class II (LEV) as the modern drug of choice …14% preferred class I (BZ) …28% preferred a combination of these two classes "Most of respondents preferred Nilzan plus (levamisole) and Systamex (oxfendazole, a benzimidazole). The preference was for those drugs, which initiated diarrhoea, such as levamisole, believing that the diarrhoea helped to expel the worms. The majority of respondents did not rotate the dewormers (a recommendation to reduce the development of parasite resistance against the drugs) neither did veterinary officers and veterinary assistants. They changed the dewormer only after one drug showed poor results." Administration 50% used deworming after every 6 months 20% used deworming every 3 months 30% used when indicated ----- 58% of all respondents administered anthelmintics in diluted form 60% of veterinary officers were found using diluted drugs, to the satisfaction of clients who suspected that	"Veterinary officers and assistants and owners preferred to use modern anthelmintics. Traditional practitioners and farmers used indigenous homeopathic preparations, which according to them had good results (visual observation for the removal of worms). Herbal or homeopathic dewormers are available from veterinary pharmacies ("Canizole", against intestinal worms and flukes of sheep and horses; "Deworming plus" against intestinal worms, flukes and external parasites of sheep and horses; "Granil" a combination of dewormer, minerals, vitamins and active enzymes) although these products are not registered in the country."

Citation	Study location Sample size	Animal Disease	Drug/Use/Frequency	Notes
			administrating the drug in pure form (per recommendations) may lead to toxicity	
Wyatt and Grace (2013a and 2013b)	Kenya and Tanzania Sample size In Kenya, n=316 farmers; in Tanzania, n=456 farmers	Newcastle disease	In Tanzania 29% treated the chicken if suspected to have ND - 50% of these HH used traditional medicine 42% of farmers reported having ever used the NDV Of those who had used the NDV …54% reported the NDV was administered by a community vaccinator …20% reported it was administered by an extension workers …15% reported it was administered by a vet …12% reported it was self-administered …5% reported it was administered by another HH member In Kenya 64% treated the chicken if suspected to have ND - 66% of these HH used traditional medicine 34% of farmers reported having ever used the NDV Of those who had used the NDV …93% reported the NDV was administered by a village based ag advisor …4% reported it was administered by community vaccinator …4% reported it was self-administered	

References available on request

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Annex 2 Reports on antibiotic use

Country	Income 2010	Poultry x1000	Sheep & Goats	Pigs	Cattle	AB ton	Ab G/VLU	Year	Source
Iceland	High	218	480,284	40,016	73,781	1	6.25	2010	EMA
Norway	High	4,412	2,375,791	850,383	874,535	6	3.98	2010	EMA
Latvia	High	4,829	83,900	376,500	378,200	7	10.59	2010	EMA
Estonia	High	1,824	80,400	365,100	234,700	8	17.14	2010	EMA
Slovenia	High	3,052	168,004	415,230	472,878	8	11.54	2010	EMA
Sweden	High	7,808	564,900	1,519,900	1,536,700	14	5.80	2010	EMA
New Zealand	High	13,841	32,657,881	335,114	3,600,000	57	7.95	2010	MPI
Cyprus	High	4,330	435,212	463,932	55,522	57	152.81	2011	EMA
Switzerland	High	8,966	512,249	1,583,290	1,602,820	58	22.92	2010	EMA
Austria	High	16,338	429,800	3,134,000	2,013,280	62	16.37	2010	EMA
Czech Republic	High	25,067	228,409	1,907,990	1,328,930	71	27.77	2010	EMA
Ireland	High	15,760	4,651,700	1,518,300	6,606,600	96	12.02	2010	EMA
Denmark	High	14,546	159,626	13,173,100	1,571,050	119	14.30	2010	DANMAP
Portugal	High	46,500	3,393,000	2,324,900	1,391,100	181	53.90	2010	EMA
Hungary	High	40,284	1,281,000	3,247,000	700,000	206	72.17	2010	EMA
Belgium	High	34,830	142,000	6,430,000	2,593,000	299	48.46	2010	EMA
United Kingdom	High	170,245	31,084,500	4,423,000	9,901,000	456	26.94	2010	EMA
Netherlands	High	103,438	1,544,000	12,252,000	650	461	63.02	2010	EMA
Poland	High	131,866	380,385	14,865,300	5,723,940	479	33.00	2011	EMA
Australia	High	86,447	72,585,500	2,289,290	26,733,000	644	17.89	2009-2010	APVMA
Japan	High	286,003	27,000	9,800,000	4,376,000	656	54.04	2010	MAFF
Rep Korea	High	158,215	263,000	9,880,630	3,351,390	843	85.19	2010	QIA
France	High	172,741	9,325,580	14,531,900	19,620,900	997	33.74	2011	EMA
Spain	High	138,905	21,485,400	25,342,600	6,075,100	1,746	78.35	2010	EMA
Italy	High	154,000	8,973,600	9,157,100	6,447,000	1,928	143.21	2010	EMA
Germany	High	128,899	2,238,476	26,509,000	12,809,500	2,002	72.60	2010	EMA
USA	High	2,351,088	8,658,000	64,887,000	93,881,200	13,542	89.86	2011	FDA
Kenya	Low	30,398	23,191,000	347,400	17,862,900	15	0.73		Paper
Philippines	LM	170,227	4,207,700	13,397,800	5,841,300	1,244	84.84		Paper
Thailand	LM	261,421	423,416	7,623,730	8,120,650	12,417	851.12		Paper
China	LM	5,921,786	284,727,767	476,237,000	107,400,295	200,000	461.67		Paper
Lithuania	UM	9,309	67,200	928,200	759,400	16	12.09	2010	EMA
Bulgaria	UM	17,354	1,761,072	729,798	571,311	46	35.93	2011	EMA
Russ.	UM	403,793	21,988,200	17,231,000	20,681,840	47	1.32		Paper
Chile	UM	75,979	4,394,350	2,706,150	3,900,000	450	69.74		Paper
Iran	UM	511,600	79,700,000		9,150,000	1,000	44.97		Paper
South Africa	UM	126,535	30,775,850	1,594,490	13,731,000	1,500	79.49		Paper

Grams of antibiotics used in the production of one livestock unit

	0 to 10 grams per TLU	11-40 grams per TLU	41-100 grams per TLU	>200 grams per TLU
High income (2010)	Norway, Iceland, New Zealand, Sweden	Australia, Ireland, UK, Switzerland, France	Japan, Germany, Spain, Hungary, Netherlands, Korea, USA,	Italy, Cyprus
Developing (2010)	Russian Federation, Kenya	Lithuania, Bulgaria	Iran, South Africa, Philippines, Chile (in fish)	China, Thailand

References available on request

Annex 3 Market Report Summary: 2013

Executive Summary

According to market research, the global animal antimicrobials market was valued at just over $3 billion in 2013 and is expected to reach $4 billion by 2018. The market is highly consolidated and dominated by a small number of North American and European firms. Challenges include the increased demand for regulatory bans and concerns over animal production and welfare while growing livestock numbers and increasing demand for animal protein are driving increases in demand for antimicrobials. The current focus in developed markets in North America and Europe but this is expected to shift to high growth markets in Asia and other developing countries. Globally, there is a shortage of new antibiotics in the pipeline of major pharmaceutical companies owing to low returns on investment on the animal antimicrobial products.

By product type, tetracyclines continue to remain the leading category, accounting for around half the market in 2015 and with strong growth potential. The penicillins and sulfonamides segments are also large markets with shares of 14.9% and 10.7%, respectively, in 2013. The pig sector dominates the global animal antimicrobials and antibiotics market, accounting for a market share of approximately one quarter and growing fast. This segment is also poised to grow at a higher rate during the forecast period.